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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,131	12/08/1999	VALERIE CHEYNET-SAUVION	104458	5581

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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	25

DATE MAILED: 08/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,131	CHEYNET-SAUVION ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-41 and 43-68* is/are pending in the application.

4a) Of the above claim(s) *48-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-41 and 43-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). 22 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Supplemental Office action

1. The following is a supplemental Office action to that which was mailed on 30 July 2002. The period for response is restarted from the date of mailing of the instant Office action.

Location of Application

2. The location of the subject application has changed. The subject application is now located in Group 1630, Art Unit 1634.

Continued Prosecution Application

3. The request filed on 16 January 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/402,131 is acceptable and a CPA has been established. An action on the CPA follows.

Election/Restrictions

4. In Paper No. 12 applicant was required to elect between inventions groups into Groups I, II, and III. Applicant, in their response of 03 November 2000, Paper No. 13, elected the invention of Group I, claims 35-47. Claims 35-41 and 43-47 most closely parallel the originally elected invention. Accordingly, said claims 35-41 and 43-47 will be examined in the instant application.

5. Claims 48-68 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. A response to the traversal was provided in the Office action of 05 December 2000, Paper No. 14, and was made FINAL. Applicant, at page 5 of the response received 15 April 2002 reiterates their reasons of traversal of the rejection. Said argument has no been found persuasive for reasons already of record.

6. This application contains claims 48-68 drawn to an invention nonelected with traverse in Paper No. 13 and 21. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Drawings

7. New corrected drawings are required in this application because applicant, effective May 3, 2001, can no longer hold in abeyance the submission of corrected formal drawings. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 35-41 and 43-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claim 1 with the added limitation that the RNA polymerase is that of T7 RNA polymerase R627A, does not reasonably provide enablement for the use of any other RNA polymerase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Quantity of Experimentation Necessary

The quantity of experimentation needed is tremendous. The claimed method is predicated upon the discovery that a point mutation resulted in different properties of T7 RNA polymerase. In order for one of skill in the art most closely associated with the invention make and use other such RNA polymerases, said skilled artisan would need to undertake screenings of potentially millions of modified polymerases in the hopes of finding even pone other that will function as claimed. Such efforts, however, would be undertaken with little if any reasonable expectation of success. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
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> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

Unlike the situation in *Genentech*, the subject specification does provide one example. However, the subject application is analogous to *Genentech* as it relates to the use of other alternative RNA polymerases. Accordingly, applicant is urged to consider narrowing the scope of the claims to those embodiments adequately supported by the disclosure.

The Amount of Direction or Guidance Provided

The specification provides very limited guidance. More specifically, only one modified RNA polymerase has been disclosed and which functions in the required of the claimed method.

The Presence or Absence of Working Examples

The specification has been found to provide three examples of which only one is related to the claimed method. That method, Example 2 (pages 29-31), is directed to the use of mutated T7 RNA polymerase R627A.

It is further noted that T7 RNA polymerase is a DNA-dependent RNA polymerase. As presently worded, the claim requires the use of an RNA-dependent RNA polymerase. The examiner is not certain if this is a typographical error or whether the dependency of the RNA polymerase has been changed.

The Nature of the Invention

The claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The State of the Prior Art

The state of the prior art is undeveloped as it relates to the identification and use of modified RNA polymerases that can function as required of the claimed method.

The Relative Skill of Those in the Art

The relative skill in the art is high, on par with those that hold a Ph.D. in biochemistry.

The Breadth of Scope of the Claims

The claims have sufficient breadth of scope so to encompass virtually RNA polymerase that can function in the claimed method.

For the above reasons, and in the absence of convincing evidence to the contrary, applicant is again urged to consider narrowing the scope of the claims to those embodiments adequately supported by the disclosure.

Response to argument

10. Applicant asserts at page 6 of the response of 15 April 2002, hereinafter the response, that thy have discovered a "family of RNA polymerase" that has the capacity to act as an RNA-dependent RNA polymerase when they have been known in the art to act as a DNA-dependent RNA polymerase and that they have further found that by mutating the RNA polymerases that they have obtained RNA polymerases that are capable of synthesizing a transcriptional product from an RNA template with a better yield than from a DNA template."

11. The above argument has been fully considered and has not been found persuasive towards the withdrawal of the rejection. Agreement is reached in that applicant has found two heretofore art-recognized DNA-dependent RNA polymerases that can synthesize RNA from an RNA template: T3 and T7; see page 12, lines 33-35. However, this discovery does not extend to all known DNA-dependent RNA polymerases. Further, page 16 of the disclosure teaches explicitly that the modified RNA polymerase requires a double-stranded DNA promoter sequence. The claims are not limited to this embodiment, nor are the claims limited to those RNA polymerases (T3 and T7) that have been shown to exhibit this unexpected property.

12. At page 7 of the response argument is presented that T3, T7 and SP6 are the members of the family of RNA polymerases that exhibit this property. As noted above, however, the specification teaches explicitly that only T3 and T7 have exhibited this property. The specification does teach at page 4 that T3, T87 and SP6 are perhaps the simplest and best-known RNA polymerases. However, the aspect of being a simplistic or well-characterized RNA polymerase does not support the position that all three have been shown to exhibit this unexpected property.

13. At page 10 of the response argument is advanced that the specification enables the production of mutated RNA polymerases according to claim 48 (non-elected).

14. Also at page 7 of the response argument is advanced in that these art-recognized DNA-dependent RNA polymerases are in fact RNA-dependent RNA polymerases has not been found to be persuasive. As noted above, the specification teaches that these RNA polymerases (T3 and T7) still require a double-stranded DNA promoter region even when producing an RNA transcript from an RNA sequence. While there may be regions of similarity between different

members of the family of polymerases, such does not adequately enable the use of alternative polymerases as enzyme activity and alterations in amino acid structure are anything but predictable. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which can be tolerated in a protein's amino acid sequence and still retain similar biological activity requires a (1) knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which re conserved (*i.e.*, expectantly intolerant to modification), and (2) detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determination to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the real of routine experimentation. Acknowledgement is made of where claim 35 refers to a "consensus sequence from position -17 to -1." Such reference to a "consensus sequence," however, has not been found to sufficiently narrow the scope of the claims as the "consensus sequence" is not defined in the specification by a SEQ ID NO. Accordingly, just what constitutes the "consensus sequence" and how that sequence is to be modified, and in terms related back to the requisite RNA polymerases is nebulous at best.

15. While argument is again advanced in that the specification is enabling for the production of other polymerases, such claims are not under consideration before the Office. It is well settled that one cannot enable the use of that which they have not yet possessed. At best, applicant's disclosure may support claims drawn to a method of making other such RNA polymerases. With the specification teaching explicitly that but two "simplistic" RNA polymerases have

demonstrated this unexpected property, and that mutation to one of these two polymerases (T7) has found to have utility does not enable the use of other polymerases. To suggest that by recognizing that one polymerase has an unexpected property some how renders obvious all other such polymerases strongly counters applicant's own argument that the property is indeed unexpected.

16. One of the main considerations to be made in determining whether undue experimentation is required is the amount of experimentation required. See *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). Even if substitutions with the natural 20 amino acids encoded by DNA were the only modifications, instant claims would still broadly encompass a multitude of species; calculated as 20^N * (length)!/N/(length-N)! wherein "20" is the number of natural amino acids encoded by DNA, "N" is the number of positions where substitutions can occur, "!" is the factorial symbol, "/" is the division symbol and "length" is the total number of amino acids in the protein or peptide. In putting these numbers in perspective, it is noted that the earth is estimated to have existed for 10^{17} seconds (see Creighton, T.E. 1983. Proteins: Structure and Molecular Principles, W. H. Freeman and Company, NY. 93-94, page 94, paragraph 1). There are an estimated 10^{79} atoms in the universe (see page 231 of Creighton, Prog. Bophys. Molec. Biol. 33:231-233, 1975). A polypeptide chain of 100 amino acids could exist in 10^{130} combinations and "just one molecule of each of these different proteins would fill the entire [known] universe 10^{27} times over, even if packed together in the most efficient manner" (see paragraph 1, page 94 of 1983 Creighton reference).

17. While recombinant and mutagenic techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within

the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar biological activity are limited in any protein. The result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modifications in such proteins.

18. The specification does not support the broad scope of the claims which encompass all modifications and fragments because the specification does not disclose the following:

a) Alternative amino acid sequences for the RNA polymerase;

b) The general tolerance to modification and extent of such tolerance;

c) The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;

d) What fragments, if any, can be made which retain the biological activity of the intact protein/RNA polymerase; and

f) The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims, broadly including any number of additions, deletions, or substitutions and fragments of any size. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

" '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').

"Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
"It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

19. For the above reasons, and in the absence of convincing evidence to the contrary, applicant is again urged to consider narrowing the scope of the claims to those embodiments identified as being adequately supported by the disclosure.

Conclusion

20. This is a CPA of applicant's earlier Application No. 09/402,131. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

21. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization

where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

23. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
August 14, 2002